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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Permethrin

FROM: Esther Rinde, Ph.D. Esther Rinde 3/8/89
Science Analysis and
Coordination Branch
Health Effects Division (TS-769c)

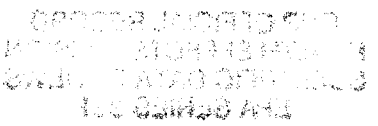
TO: George LaRocca
Product Manager #15
Registration Division (TS-767c)

The Health Effects Division Peer Review Committee met on Dec. 12, 1988 to discuss and evaluate the weight-of-the-evidence on Permethrin, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William L. Burnam	William L Burnam
Robert Beliles	Robert Beliles
Reto Engler	Reto Engler
Judith Hauswirth	Judith W. Hauswirth
Kerry Dearfield	Kerry L Dearfield
Richard Levy	Richard A. Levy
Marion Copley	Marion Copley
Jack Quest	John A. Quest
William Sette	William Sette
Esther Rinde	Esther Rinde



A. 2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

John Doherty

Edwin Budd

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Richard Hill —

Diane Beal

Marcia Van Gemert

George Ghali

Lynnard Slaughter

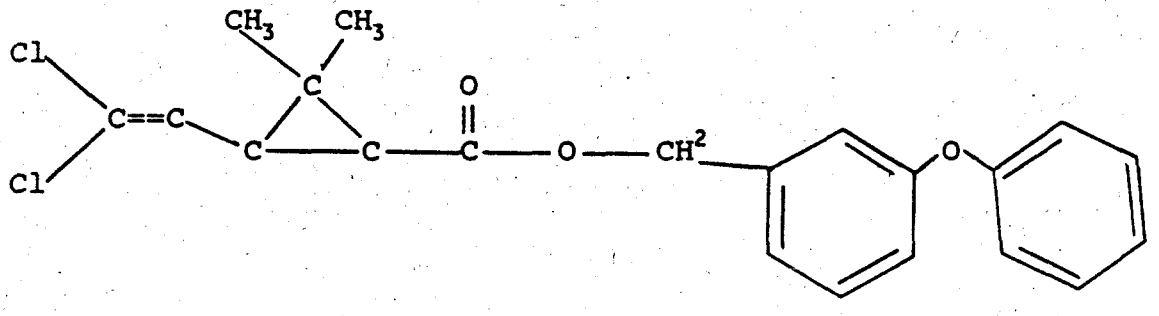
B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Doherty and the Paynter/Budd/Litt document: "Permethrin, Assessment of Chronic and Oncogenic Effects, A Summary" (Sept. 3, 1982); Tables and statistical analysis by B. Fisher (Memo, Sept. 13, 1988, amended 2/28/89). The material reviewed is attached to the file copy of this report.

C. Background Information:

Permethrin is a pyrethroid insecticide which has been considered by the Agency to be oncogenic based on findings summarized in the Paynter/Budd/Litt document (9/3/82). It had not been peer reviewed by the Health Effects Division Peer Review Committee (or its predecessor in the former Toxicology Branch of the Hazard Evaluation Division).

Structure of Permethrin:



D. Evaluation of Oncogenicity Evidence for Permethrin:

I. RAT STUDIES

1. Burroughs-Wellcome Oncogenicity Study in the Rat.

Reference: The Wellcome Foundation; Lab.# HEFG 80-33. July 2, 1980.

Permethrin (25% cis/75% trans) was administered in the diet to groups of 60 male and 60 female Wistar rats at 0 (control), 10, 50 or 250 mg/kg/day for 2 years. No evidence of an oncogenic response attributable to the ingestion of Permethrin was reported in this study.

Non-oncogenic effects, all at the HDT (250 mg/kg/day) included; occasional body tremors in both sexes; increased liver weights in males; hepatocyte hypertrophy in both sexes and disturbances in thyroid follicular cell growth pattern in both sexes. These effects were not considered to be life-threatening. In Males only, increased mortality at the HDT was reported. Thus, although an adequate dose was reached in males, there was no evidence that the females were tested at a high enough dose to adequately assess the oncogenic potential of Permethrin.

2. ICI Oncogenicity Study in the Rat.

Reference: Report # CTL/p/357. Central Toxicology Laboratory, ICI. England, November, 1977.

Permethrin (40% cis/60% trans) was administered in the diet to groups of 60 male and 60 female Wistar rats at 0 (control), 500, 1000 or 2500 ppm (equivalent to 0,25,50 or 125 mg/kg/day, respectively) for 2 years. No evidence of an oncogenic response attributable to the ingestion of Permethrin was reported in this study.

Non-oncogenic effects included: increased liver weights in both sexes at 1000 and 2500 ppm and in males only at 500 ppm; increased liver enzyme (aminopyrine-N-demethylase) activity in both sexes at 1000 and 2500 ppm; increased kidney weights in males at all treatment levels, and increased pituitary weights in males at 1000 and 2500 ppm. These effects were not considered to be life-threatening. There was also increased mortality in males (decreased mortality in females) at the HDT (2500 ppm/125 mg/kg/day). Thus, although an adequate dose was reached in males, there was no evidence that the females were tested at a high enough dose to adequately assess the oncogenic potential of Permethrin.

D. Evaluation of Oncogenicity Evidence for Permethrin (contd.):

I. RAT STUDIES (contd.)

3. FMC Oncogenicity Study in the Rat.

Reference: Project # 74R-1022; Bio/Dynamics Inc., November, 1977.

Permethrin (40% cis/60% trans) was administered in the diet to groups of 60 male and 60 female Long-Evans rats at 0 (control), 20, 100 or 500 ppm (equivalent to 0,1,5 or 25 mg/kg/day, respectively) for 2 years.

Initially, an increased incidence of adenomas and adenocarcinomas, which was not statistically significant, was reported in the lungs of male rats. The same lung slides were re-read by a second pathologist; based on these readings, there was a statistically significant increase in lung neoplasms in males at the mid and high dose. Subsequently, all available lung tissues from the male rats were step-sectioned at 250 micron intervals and read again by the original pathologist, who then reported revised incidences, which were again not statistically significant.

"In an effort to resolve the dilemma of which figures to use, Toxicology Branch made additional theoretical calculations of lung tumor incidence, based on equal amounts of lung tissue (adjusted) from all control and test groups." [Paynter et al., 1982].

Table 1 shows the lung tumor incidences as given in each of the above described assessments. (Historical control data for lung tumor incidence in this strain of rat was not available).

Non-oncogenic effects were slight increases in liver weights of male rats at 100 ppm, which became more definite at 500 ppm.

The Committee considered the evidence for lung tumors in these male rats to be equivocal. The Committee also agreed that based on the absence of significant toxic effects (other than the slight increases in liver weight in males) these rats were not tested at a high enough dose to assess the oncogenic potential of Permethrin.

D. Evaluation of Oncogenicity Evidence for Permethrin (contd.):

Table 1. Lung tumors in the FMC Rat Study.

	Males				
				Area Adjusted	
Dose Level (ppm)	Original Analysis	Reassessment (by 2nd Pathologist) (250 u	After Step Sectioning (250 u intervals)	Original Analysis	All Slides
0	1/59	1/60	8/60	1/60	8/60
20	3/57	3/57	6/57	2/57	8/57
100	6/57	8/60*	10/60	5/60	15/60[b]
500	5/56	6/60*	10/60	4/60	14/60[b]

Data are incidence of tumors/number of animals examined.
*Statistically significant $p < 0.05$.
[b] borderline statistical significance, p approximately 0.10.

II. MOUSE STUDIES

1. FMC Mouse Oncogenicity Study #1 (BioDynamics Laboratory, 1978)

This study was determined to be invalid, based on reports that there were test diet feeding errors for a significant portion of the study and because of misplaced animals and failure to positively identify misplaced animals.

D. Evaluation of Oncogenicity Evidence for Permethrin (contd.):

2. FMC Mouse Oncogenicity Study #2

Reference: Project # 76-1695; Bio/Dynamics, Inc. Oct. 9, 1979.

Permethrin (unspecified) was administered in the diet to groups of 75 male and 75 female Charles River CD-1 strain mice for 2 years. Male mice were dosed with 0 (control), 20, 500 or 2000 ppm (equivalent to 0,3,71, or 286 mg/kg/day, respectively); female mice with 0 (control), 20, 2500 or 5000 ppm (0,3,357, or 714 mg/kg/day, respectively).

The following neoplastic lesions were reported:

Statistically significant increases in liver adenomas in male mice at all doses (and outside historical control range at all doses) with a significant dose-related trend; statistically significant increases in combined[1] liver adenoma/carcinoma at mid-and high-dose in males.

Statistically significant increases in liver adenomas in female mice at the mid- and high-dose (both were outside historical control range) with a significant dose-related trend; statistically significant increases in combined[1] liver adenoma/carcinoma at mid- and high-dose, with a significant dose-related trend.

Statistically significant increases in lung adenomas and combined adenoma/carcinoma at all doses in females; carcinomas were significantly increased at HDT only, but were increased at all doses. The incidences of adenoma and carcinoma were outside historical controls at mid- and high-dose (carcinomas only slightly so at mid-dose). There were also significant dose-related trends for lung adenomas, carcinomas and combined adenoma/carcinomas in females.

The incidences of lung tumors in male mice (adenoma or carcinoma, or combined) were not statistically significant at any dose, nor was there a dose-related trend for any of them.

Tumor incidences are given in Tables 2-5 and are based on a re-reading of the slides by Dr. L.K. Ackerman (E.P.L.).

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[1]Combined incidences for both male and female liver tumors reflected only the increase in adenomas, ie: liver carcinoma incidence in males was somewhat increased (not statistically significant) over concurrent controls at the mid-dose only and were actually less than controls at all other doses; in the case of females incidences in all dose groups were less than that of concurrent control.

Table 2

Permethrin, FMC Mouse Study #2
Male Liver Tumor Rates[1]
and Peto Prevalence Test Results

Tumor	Dose (ppm) 0	20	500	2000
Adenoma	6/66	17/63	15/63	17/57
(%)	(9)	(27)	(24)	(30)a
p =	0.0035**	0.0052**	0.0157*	0.0001**
Carcinoma	16/68	12/64	19/64	8/60
(%)	(24)	(19)	(30)b	(13)
p =	0.1491	0.2756	0.1109	0.1398
Both	22/68	29/64	34/64	25/60
(%)	(32)	(45)	(53)	(42)
p =	0.1145	0.0633	0.0099**	0.0411*

[1]Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.
aFirst adenoma at week 56.
bFirst carcinoma at week 47.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Historical Control Liver Tumor Data* in the FMC Mouse #2 Study (Males)

Adenoma	Carcinoma	Combined
6.1(0-11.7)%	7.9(1.7-12.8)%	14.0(5.3-20.0)%

*Historical control data are presented as the mean and the range from nine studies as submitted by the BioDynamics Laboratory in the fall of 1988.

Table 3

Permethrin, FMC Mouse Study #2
Female Liver Tumor Rates[1]
and Cochran-Armitage Trend and Fisher Exact Test Results

Tumor	Dose (ppm) 0	20	2500	5000
Adenoma	2/66	4/62	22/63	28/65
(%)	(3)	(6)	(35)a	(43)
p =	0.0000**	0.2994	0.0000**	0.0000**
Carcinoma	4/49	3/55	3/49	2/51
(%)	(8)	(5)	(6)	(4)
p =	0.2534	0.4312	0.4938	0.3082
Both	6/66	7/62	25/63	30/65
(%)	(9)	(11)	(40)	(46)
p =	0.0000**	0.4519	0.0000**	0.0000**

1Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.
aFirst adenoma at week 54.
bFirst carcinoma at week 81.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Historical Control Liver Tumor Data* in the FMC Mouse #2 Study
(Females)

Adenoma	Carcinoma	Combined
3.0(0-7.8)%	1.3(0-4.9)%	4.3(1.1-11)%

*Historical control data are presented as the mean and the range from nine studies as submitted by the BioDynamics Laboratory in the fall of 1988.

Table 4

Permethrin, FMC Mouse Study #2
Male Lung Tumor Rates[1]
and Peto Prevalence Test Results

Tumor	Dose (ppm) 0	20	500	2000
Adenoma	16/73	15/71	15/68	17/69
(%)	(22)	(21)	(22)a	(25)
p =	0.1186	0.4650	0.4970	0.1534
Carcinoma	7/49	5/53	13/54	4/31
(%)	(14)	(9)b	(24)	(13)
p =	0.4100	0.2081	0.1096	0.4615
Both	23/73	20/71	28/68	21/69
(%)	(32)	(28)	(41)	(30)
p =	0.1321	0.3639	0.1505	0.1752

[1]Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.
aFirst adenoma at week 25.
bFirst carcinoma at week 81.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Historical Control Lung Tumor Data* in the FMC Mouse II Study. (males)

Adenoma	Carcinoma	Combined
4.0(0-10.4)%	7.7(4.0-14.3)%	13.5(6.5-22.4)%

*Historical control data are presented as the mean and the range from nine studies as submitted by the BioDynamics Laboratory in the fall of 1988.

Table 5

Permethrin, FMC Mouse Study #2
Female Lung Tumor Rates[1]
and Cochran-Armitage Trend and Fisher Exact Test Results

Tumor	Dose (ppm) 0	20	2500	5000
Adenoma	9/71	17/68	24/68	29/69
(%)	(13)	(25)	(35)a	(42)
p =	0.0002**	0.0495*	0.0015**	0.0001**
Carcinoma	6/66	7/62	11/59	15/62
(%)	(9)	(11)b	(19)	(24)
p =	0.0047**	0.4519	0.0977	0.0187*
Both	15/71	24/68	35/68	44/69
(%)	(21)	(35)	(52)	(64)
p =	0.0000**	0.0473*	0.0002**	0.0000**

[1]Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.
aFirst adenoma at week 39.
bFirst carcinoma at week 62.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Historical Control Lung Tumor Data* in the FMC Mouse II Study. (females)

Adenoma	Carcinoma	Combined
5.0(0-20.4)%	8.5(2.0-16.0)%	13.5(6.5-22.4)%

*Historical control data are presented as the mean and the range from nine studies as submitted by the BioDynamics Laboratory in the fall of 1988.

D. Evaluation of Oncogenicity Evidence for Permethrin (contd.):

II. MOUSE STUDIES (contd.)

3. Burroughs-Wellcome Mouse Oncogenicity Study

Reference: The Wellcome Foundation; Lab.# HEFG 80-29, Dec. 1980.

Permethrin (25% cis/75% trans) was administered in the diet to groups of 75 male and 75 female (100 mice/sex for control) CFLP strain (Swiss derived) mice at 0 (control), 10, 50 or 250 mg/kg/day for 92 weeks.

The following neoplastic lesions were reported: statistically significant increase in lung tumors at the highest dose in females, with a significant dose-related trend. Malignant tumors were observed in treated animals (1 in mid- and 2 in high-dose group) while none were seen in controls). The tumor incidences were, however, within the historical range (Table 6).

Non-neoplastic effects, noted at the HDT only (250 mg/kg/day) included: slightly increased liver and kidney weights, and cuboidal/columnar metaplasia of alveolar epithelium in lungs (adaptive effects only). The Committee concluded that these mice were not tested at a high enough dose to assess the oncogenic potential of Permethrin.

Table 6. Mice with One or More Adenomatous Tumors in the Lungs in the Burroughs-Wellcome Mouse Study.

Dose Group (mg/kg/day)	Males		Females	
	Incidence	Percent	Incidence	Percent
0	26/99	26.3	3/96	3.1
10	14/75	18.7	5/71	7.0
50	17/73	23.3	7/74	9.5
250	16/74	21.6	15/74*	20.3*
Hist. Control[1]			20.4(7.5-30.0%)	

* statistically significantly different from control group, $p < 0.05$.

[1]Historical control data (mean and percentage range) derived from 9 studies containing 807 female CFLP control mice and include mice affected with lung adenomas and carcinomas.

D. Evaluation of Oncogenicity Evidence for Permethrin (contd.):

II. MOUSE STUDIES (contd.)

4. ICI Mouse Oncogenicity Study

Reference: Report # CTL/P/358 and CTL/P/359; Central Toxicology Laboratory, ICI; Jan. 27, 1978.

Permethrin (40% cis/60% trans) was administered in the diet to groups of 70 male and 70 female Alderly Park strain (Swiss derived) mice at 0 (control), 250, 1000, or 2500 ppm (equivalent to 0,36,143 or 357 mg/kg/day) for 98 weeks.

A slight increase in lung adenomas in males at the HDT (2500 ppm) which was not statistically significant was reported. There were no carcinomas observed in any of the male groups; in female mice, one carcinoma was reported in each treatment group.

Table 7 presents the lung tumor incidences for this study. (Historical control data were not available.)

Non-oncogenic effects noted at 1000 ppm and above, included minimal changes in liver enzyme activity, increases in liver weight and histopathological changes in the liver (eosinophilia of hepatocytes). At the HDT (2500 ppm) there was increased mortality in both sexes. This study was conducted at an adequate dose for determining the oncogenic potential of Permethrin.

Table 7. Adenomas in Mouse Lungs in the ICI Mouse Study

Dose Level (ppm)	Males		Females	
	Incidence	Percent	Incidence	Percent
0	11/70	15.7	11/70	15.7
250	6/70	8.6	8/70	11.4
1000	13/70	18.6	10/70	14.3
2500	17/70[a]	24.3	15/70	21.4

[a]Fisher's Exact Test p = 0.145 (not significant).

D. Other Studies: Shimkin Mouse Lung Bioassay (Biocon, Rockville, MD., 1985)

Groups of 16 male and 16 female strain A/J mice were dosed with either 0 (control), 285, 475 (females only), 713.5 or 1425 mg/kg permethrin (40% cis/60% trans) for three days a week for eight weeks. A separate positive control group was dosed with urethane (1000 mg/kg). Animals were sacrificed after 24 weeks and their lungs examined for tumors. The frequency of tumors in the permethrin treated mice was equivalent to the corn oil and untreated control groups. Urethane produced the expected response. No evidence that permethrin promoted lung tumors in this study was generated.

1. Metabolism

There are several studies which indicate that permethrin is rapidly absorbed from the gastrointestinal tract, metabolizes primarily by attack at the ester site, after which the metabolites are conjugated and excreted in the urine. Only trace amounts of radiolabelled material remain in the tissues.

2. Mutagenicity

The available evidence has not demonstrated permethrin to possess any evidence of mutagenicity. Table 8 summarizes the studies available.

Other Genotoxic Effects.

No studies are available.

Additional mutagenicity studies are required, especially studies to complete the categories of structural chromosomal aberrations and other genotoxic effects. Dr. Mauer has also recommended that one or more cell transformation assays with permethrin be conducted and submitted.

3. Developmental and Reproductive Effects

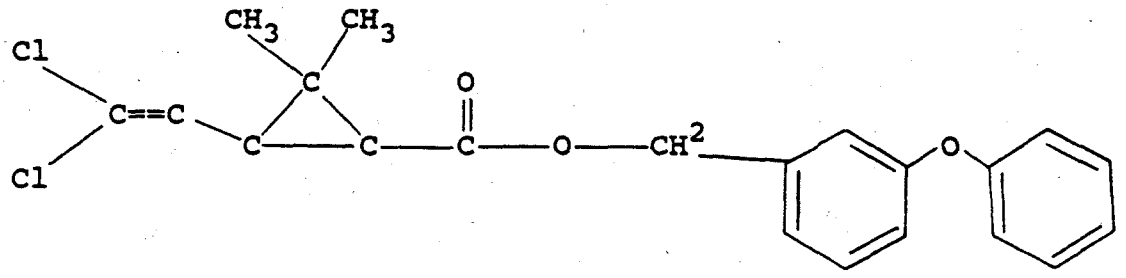
The available evidence (several teratology and multi-generation reproduction studies) has not demonstrated specific developmental toxicity resulting from permethrin treatment.

Table 8. Summary of Mutagenicity Studies with Permethrin.

Gene Mutation.		
Ames Test Litton Bionetics #2575, Dec. 1975	S.typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and S. cerevisiae strain D4 were tested over the range of 0.001 to 5.0 ul/plate.	Not mutagenic with and without metabolic activation.
Ames Test SRI #LSC4768, Jan, 1976.	S.typhimurium strains TA1535, TA1537, TA1538 TA98 and TA100 and E. coli strain WP2 were tested over the range of 1 to 1000 ug/plate.	Not mutagenic with and without metabolic activation.
Mouse lymphoma Assay. Wellcome Foundation #TTEP/77/0007, Jan. 19, 1977.	Cultures of L578Y/TK+/- mouse lymphoma cells were tested over the range of 31-125 ug/ml.	Not mutagenic with and without metabolic activation. 47 ug/ml highest working concentration.
Structural Chromosomal Aberrations.		
Dominant Lethal Wellcome Research Laboratories. HEFG 75-10, Nov. 27, 1975 and HEFG 76-2 Feb. 17, 1976.	Permethrin tested at 285 and 452 mg/kg /day.	No evidence of any dominant lethal effect. (Considered questionable by I. Mauer).
Dominant Lethal Omni Research # Daad 05-84-M-L186 June-July 1988.	Permethrin tested at 26, 130 and 260 mg/kg/day.	No evidence of any dominant lethal effect. (Considered unacceptable by I. Mauer).

E. 4. Structure-Activity Correlations

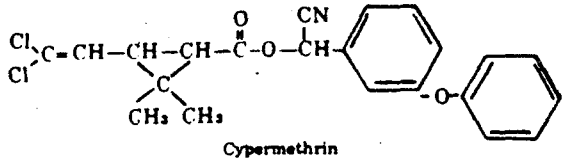
Permethrin is a pyrethroid represented by the following chemical structure:



Cypermethrin, the alpha cyano analog of permethrin, has previously been peer reviewed by TB (memo 9/6/88). Cypermethrin was concluded to be a category C oncogen based on increased incidence of benign lung tumors in female mice (alveologenic adenoma). The Peer Review Committee concluded that quantitative risk assessments need not be determined for the individual registrations and tolerances for cypermethrin.

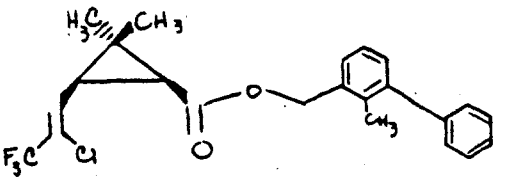
Bifenthrin is another pyrethroid which has been peer reviewed by TB (memo 2/2/87) and was also characterized as a category C oncogen. The Committee unanimously concluded that a quantitative risk assessment should be developed for Bifenthrin. Bifenthrin has a trifluoro methyl group in place of a chlorine on the vinyl moiety and the alcohol side chain is a dibenzyl methyl rather than a phenoxy benzyl group. Bifenthrin was determined to be associated with increased incidence of liver (in males), lung (in females) and urinary bladder leiomyosarcomas (in males) in mice.

SAP agreed with the C classification for Bifenthrin, but disagreed with the call for quantification of risk, because there was no dose-response. The Peer Review Committee in its second meeting (memo 6/9/88) argued both for and against quantification, but favored quantification based on the uncommon nature of the tumor type (urinary bladder leiomyosarcomas). Arguments against quantification were that bladder tumors were seen only in male mice, only at the highest dose tested and supporting SAR information (permethrin, cypermethrin) had not yet been fully evaluated by the Peer Review Committee.



Cypermethrin

Bifenthrin



F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on permethrin to be of importance in a weight-of-the-evidence determination of oncogenic potential.

> The available data base for the oncogenicity of permethrin consisted of 7 long-term studies (one of which was deemed invalid). There were 3 rat studies: two in the Wistar rat and one in the Long Evans rat. There were 3 (valid) mouse studies: 1 in the Charles River CD-1 strain, 1 in the CFLP strain and 1 in the Alderly Park strain.

There was no evidence of oncogenicity in either study using the Wistar rat. Female rats did not receive adequate doses of permethrin to assess oncogenic potential.

The evidence in the Long-Evans Rat study was equivocal; rats (both sexes) did not receive adequate dose.

There was clear evidence of oncogenicity in the female CD-1 mouse (FMC) which consisted of:

In female mice

Statistically significant increases in liver adenomas at the mid- and hi-dose (both were outside historical control range[2]) with a significant dose-related trend.

Statistically significant increase in lung adenomas and combined adenoma/carcinoma at all doses; carcinomas were significantly increased at HDT only, but were increased at all doses. The incidences of adenoma and carcinoma were outside historical controls[2] at mid- and high-dose (carcinomas only slightly so at mid-dose). There were also significant dose-related trends for lung adenomas, carcinomas and combined adenoma/carcinoma.

Additionally, in male mice there were:

Statistically significant increases in liver adenomas at all doses (and outside historical control range[2] at all doses) with a significant dose-related trend.

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[2]NOTE: Historical control incidences may include animals which had both adenoma and carcinoma and thus would not directly compare with the incidences for the animals on study, in which mice with both adenoma and carcinoma were counted only as having carcinoma. Thus, the incidences in historical controls of adenoma (and combined adenoma/carcinoma) could actually be lower, and consequently the increased incidences for the animals on study might even be more significant.

F. Weight of Evidence Considerations (contd.)

The Committee noted the clear dose-response, especially for female lung adenomas in the FMC CD-1 mouse study.

The incidences of lung tumors in male mice (adenoma or carcinoma, or combined) were not statistically significant at any dose, nor was there a dose-related trend for any of them.

In the second study in the CFLP mouse (B-W) there was a statistically significant increase (within historical control range) in lung tumors at the highest dose in females, with a significant dose-related trend.

In the Alderly-Park mouse strain, a slight increase in lung adenomas in males at the HDT (375 mg/kg) which was not statistically significant was reported. There were no carcinomas observed in any of the male groups; in female mice, one carcinoma was reported in each treatment group.

Permethrin does not appear to present a concern for mutagenicity.

There are 2 structural analogs of permethrin, which were evaluated in Peer Review as Category C oncogens. Cypermethrin was not subject to risk assessment, based on increases in benign tumors (lung) in one sex (females). Quantitation of risk for Bifenthrin was favored by the Committee, based on the uncommon nature of bladder tumors in male mice (there were also lung tumors in female mice and liver tumors in male mice).

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [FR5A 1: 33992-34003, 1986] for classifying a carcinogen were considered.

The Peer Review Committee classified Permethrin as a Category C (possible human carcinogen), based on evidence in one species (mouse). The evidence in the second species (Long-Evans rat) was considered to be equivocal, but suggestive. The Committee also called for a quantitative risk assessment for Permethrin, based on: 2 tumor types (liver and lung) of which one (lung) was malignant, the dose-related response seen in the mouse, suggestive evidence in the Long-Evans rat, and supportive SAR information.

> A discussion was held on whether or not to repeat the rat study in order to remove the ambiguity of possible lung tumors in the second species. However, it was concluded that since an adequate risk assessment can be performed on the available data in the mouse, a repeat rat study was not necessary at this time[3].

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[3]This is also in keeping with the Agency's policy concerning animal welfare and its continued efforts to reduce the impacts on animals of EPA's testing requirements.

ADDENDUM

COMPARISON OF THE PAYNTER et al. AND PEER REVIEW COMMITTEE EVALUATIONS OF THE ONCOGENICITY OF PERMETHRIN.

The differences between the Paynter et al. (Paynter) and Peer Review Committee (PRC) evaluations of the oncogenicity of Permethrin can be attributed to the following factors.

1. At the time of the Paynter review (1982), the Agency did not have Guidelines for Carcinogen Risk Assessment, which were not issued until 1986.

Paynter applied 3 different systems for ranking and classifying the evidence, only one of which (those of the International Agency for Research on Cancer (IARC)) had general acceptance. Using the IARC classification, it was concluded " that the evidence for Permethrin must fall into the limited classification"

Applying the Agency Guidelines, PRC came to the same conclusion regarding the overall weight of evidence, ie that the evidence was limited, which according to the Guidelines is a Category C (possible human carcinogen).

2. The MTD Policy (Feb. 1987) was also not in effect at that time.

Both Paynter and PRC considered the evidence in the rat to be suggestive; however, PRC considered it even more suggestive because dosages may not have been adequate for assessing the oncogenic potential of Permethrin in female rats (in accordance with the MTD Policy document).

3. New Data

Historical control data from the performing lab. for the FMC study (Bio/Dynamics) for lung and liver tumors in the CD-1 mouse strain were submitted to the Agency in Oct. 1988. Based on these data the results in the FMC mouse study became even more significant.

Thus, the PRC was presented with the following:

> Statistically significant increases in liver adenomas at the mid- and high-dose (both were outside historical control range) with a significant dose-related trend and statistically significant increases in lung adenomas and combined adenoma/carcinoma at all doses (carcinomas were significantly increased at HDT only, but were increased at all doses). Incidences of lung adenoma and carcinoma were outside historical controls at mid- and high-dose (carcinomas only slightly so at mid-dose). There were also significant dose-related trends for lung adenomas, carcinomas and combined adenoma/carcinoma.

Additionally, in male mice there were:

> Statistically significant increases in liver adenomas at all doses (and outside historical control range at all doses) with a significant dose-related trend; statistically significant increases in combined liver adenoma/carcinoma at mid-and high-dose in males. Incidences of lung tumors in male mice (adenoma or carcinoma, or combined) were not statistically significant at any dose, nor was there a dose-related trend for any of them.

There was also a second study (Burroughs-Welcome) in the CD-1 mouse which in itself does not constitute sufficient evidence, but was supportive of the results seen in the FMC study.

> In this second study in the CD-1 mouse (B-W) there was a statistically significant increase (within historical control range) in lung tumors at the highest dose in females, with a significant dose-related trend.

PRC noted the clear dose-response, especially for female lung adenomas in the FMC CD-1 mouse study; the evidence in the CD-1 mouse was considered convincing.

4. Structure Activity Relationships (SAR)

There are 2 structural pyrethroid analogs of Permethrin (a pyrethroid), which have been evaluated by PRC as Category C oncogens. Cypermethrin, which is a very close analog (only differs in having an alpha cyano group) produced benign lung tumors in female mice. Bifenthrin, which has a dibenzyl methyl in place of a phenoxy benzyl group as the alcohol side-chain, and has a trifluro methyl group in place of a chlorine on the vinyl moiety, was associated with increased incidence of liver (males), lung (females) and urinary bladder tumors in mice.

Neither of these evaluations were available to the Paynter group.

5. Evidence for mutagenic potential

Paynter and PRC agreed that the available evidence for Permethrin does not appear to present a concern for genotoxic effects; however, it was not until recently that mutagenicity tests on file with OPP were rigorously evaluated. Based on this recent evaluation, we have identified 2 data gaps which need to be filled (in accordance with 40CFR 158 (1984)). It is required that additional studies for structural chromosomal aberration and other genotoxic effects be submitted (Of the two available studies which detect structural chromosomal aberrations, one was considered to be unacceptable, and the results from the other were called into question). In addition it was recommended that cell transformation assays should also be submitted.

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Note:

It should be noted that this classification (for Permethrin) is based on oral studies. Inhalation and/or dermal exposure bioassays, at least pharmacokinetic studies, should be performed before the classification can be properly applied to other routes.

Robert P Belaler

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